

**REMARKS**

The Examiner rejected claims 23-24 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner rejected claim 15 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner rejected claims 10-13, 18-21 and 23-24 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221).

The Examiner rejected claims 15 and 22 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221), and further in view of Burch *et al.* (US 6,552,031) and Drug Facts and Comparison (1995 Edition, pp. 1248) and Hendeler (US 6,541,613B2).

Applicants respectfully traverse the §112 and §103(a) rejections with the following arguments.

35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 23-24 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner argues: "The claims in this application introduce negative limitation as discussed in preceding comments; namely "the low dose aspirin is not covalently attached to the COX2 inhibitor". The examiner determines that when all evidences in the original disclosure are considered and carefully reviewed, the newly added claims fail to find support in the original specification.... There is no express statement about the negative limitation that can be found in the specification. Thus, the exclusion of said elements implies the inclusion of all other elements not expressly excluded, clearly illustrating that such negative limitations do, in fact, introduce new matter. The negative limitation recited in the present claims, which did not appear in the specification filed, introduces new concepts and violate the description requirement of the first paragraph of 35 USC 112."

In response, Applicants assert that matter inherently disclosed in the specification, even if not explicitly disclosed, is not new matter. See MPEP 2163.07(a) ("By disclosing in a patent application a device that **inherently** performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, **even though it says nothing explicit concerning it.**" (emphasis added)).

Applicants assert that the limitation in claims 23-24 of "wherein the low dose aspirin is not covalently attached to the COX2 inhibitor" is inherently disclosed in Applicants' specification, so that the preceding limitation of claims 23-24 is not new matter and thus not in violation of 35 U.S.C. § 112, first paragraph.

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Covalent attachment is a form of chemical binding. Therefore, in order for the low dose aspirin to be covalently attached to the COX2 inhibitor, the low dose aspirin must necessarily be chemically attached to the COX2 inhibitor by the covalent attachment. However, Par. [0024] of Applicants' specification recites: "The combined compounds of this invention may be formulated such that, although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized." Applicants assert that it is impossible for the low dose aspirin to both be chemically attached to the COX2 inhibitor and also have minimal physical contact with the COX2 inhibitor. Therefore, the preceding citation in Par. [0024] of Applicants' specification inherently discloses the low dose aspirin to not be chemically attached to the COX2 inhibitor and thus not be covalently attached to the COX2 inhibitor.

Par. [0024] of Applicants' specification further recites: "Still another approach would involve the formulation of combined compounds in which the one compound is coated with a sustained and/or enteric release polymer, and the other compound is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose or other appropriate materials as known in the art, in order to further separate the active components. **The polymer coating serves to form an additional barrier to interaction with the other component.**" (emphasis added). In the preceding embodiment of the present invention described in Par. [0024], the active ingredients are physically isolated from each other and prevented from interacting with each other, by the polymer coating, so that the active ingredients are necessarily not in covalent contact with each other. Therefore, the preceding citation in Par. [0024] of Applicants' specification inherently discloses the low dose aspirin to not be covalently attached to the COX2 inhibitor.

Based on the preceding arguments, Applicants respectfully request that the rejection of claims 23-24 under 35 U.S.C. § 112, first paragraph be withdrawn.

**35 U.S.C. § 112, Second Paragraph**

The Examiner rejected claim 15 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner argues: "Dependent claim 11 further limits the subject matter of a previous claim 14 which was canceled. Thus, Claim 11 is vague and unclear and leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.... For the examination purpose, claim 15 is understood as being dependent on the independent claim 10.... Claim 15 recites that the therapeutic composition prepared in "an enteric coated formulation". It appears in view of the independent claim 10 that each of active ingredients of the invention is administered concurrently to the patient. In other words, said therapeutic composition is not formulated together in a single dosage unit. Since the claimed "enteric coated formulation" can be formulated when the composition is prepared in a single dosage unit, the applicant's failure to further limit the subject matter of the previous claim leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear."

In response, Applicants have amended claim 15 to depend from claim 10. Since the Examiner has Examined claim 15 as being dependent on claim 10, Applicants respectfully request that the amendment of claim 15 be entered.

As to the Examiner's allegation that claim 15 fails to further limit claim 10, Applicants argue that the recited ingredients of claim 10 could be administered concurrently in ways other than through use of an enteric coated formulation. As described in Par. [0028] of the present

patent application, "the compounds may be formulated together, in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.) as a combination product". Therefore, requiring the composition to be in an enteric coated formulation in claim 15 further limits claim 10.

Based on the preceding arguments, Applicants respectfully request that the rejection of claim 15 under 35 U.S.C. § 112, second paragraph be withdrawn.

35 U.S.C. §103(a)

The Examiner rejected claims 10-13, 18-21 and 23-24 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221).

Applicants respectfully contend that claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro, because Hedden in view of Langhoff and Shapiro does not teach or suggest each and every feature of claims 10 and 18.

A first reason why claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro is that Hedden in view of Langhoff and Shapiro does not teach or suggest the feature: "low dose aspirin in the amount of 70-85 mg".

The Examiner argues: "Langhoff teaches the use of low dose aspirin(in dosage range of 30mg-75mg) for the treatment of anti-inflammatory disorder including rheumatism and arthritis."

In response, Applicants respectfully contends that Langhoff does not teach the use of low dose aspirin(in dosage range of 30 mg-75 mg) for the treatment of anti-inflammatory disorder including rheumatism and arthritis. To the contrary, Langhoff's teaches the use of a composition in the treatment of arteriosclerosis. Applicants respectfully request that the Examiner quote specific language in Langhoff that allegedly teaches that the use of low dose aspirin in doses of 30-75 mg is effective in the treatment of inflammatory disorder.

In fact, Applicants respectfully contend that it is known in the art that low dose aspirin in doses of 30-75 mg is not effective in the treatment of inflammatory disorder, as evidenced by numerous published papers. Applicants next cite the abstract of several articles to illustrate that

much higher doses of aspirin than 30-75 mg are required for therapeutically effective treatment of inflammatory disorder.

See Calin A. "Pain and inflammation", Am J Med. 1984 Sep 10;77(3A):9-16. The abstract of the preceding reference (Calin) is as follows:

"The traditional "aspirin first" approach to the treatment of osteoarthritis and rheumatoid arthritis is undergoing serious reappraisal. Aspirin and acetaminophen are equipotent in their analgesic efficacy; however, aspirin is associated with a higher incidence of side effects. Acetaminophen should therefore be used as first-line therapy for the treatment of osteoarthritis since reduction of pain is the primary therapeutic objective. Analgesic doses of aspirin (up to 3,900 mg per day) do not produce an anti-inflammatory effect and thus are not beneficial in the treatment of rheumatoid arthritis. **Only high doses of aspirin (4 to 6 g per day) used for a sustained period produce an anti-inflammatory effect.** Since many patients with rheumatoid arthritis cannot tolerate long-term use of anti-inflammatory doses of aspirin, it may be preferable to initiate therapy with one of the newer nonsteroidal anti-inflammatory drugs."

See, Gomes I, "Aspirin: a neuroprotective agent at high doses?", Natl Med J India. 1998 Jan-Feb;11(1):14-7. The abstract of the preceding reference (Gomes) is as follows:

"Aspirin, acetylsalicylic acid, is routinely used in clinics as an analgesic, antipyretic and in the secondary prevention of stroke. These effects are caused by low doses of the drug (0.3-3.6 g/day) through the inhibition of cyclo-oxygenase, the enzyme responsible for prostaglandin synthesis. **Higher doses of aspirin (4-6 g/day) are used in the treatment of inflammatory conditions such as rheumatoid arthritis** and recent laboratory findings suggest that it could play a role in neuroprotection against glutamate excitotoxicity. This article reviews the possible mechanisms of action of high-dose aspirin in neuroprotection."



See Appelrouth DJ, Baim S, Chang RW, Cohen MH, Englund DW, Germain BF, Hartman SS, Jaffer A, Mullen BJ, Smith FE, "Comparison of the safety and efficacy of nabumetone and aspirin in the treatment of osteoarthritis in adults", Am J Med. 1987 Oct 30;83(4B):78-81. The abstract of the preceding reference (Appelrouth et al.) is as follows:

A six-month, multicenter, double-blind study compared the efficacy and safety of two therapeutic regimens in 332 patients with osteoarthritis. The patients received either 1,000 mg of nabumetone as a single bedtime dose or 900 mg of aspirin in four divided doses. At the end of the study, patients in both treatment groups showed significant improvement from baseline for all five parameters; no statistically or clinically significant differences were observed between the groups. The safety data did reveal clinically and statistically significant differences between the groups. Aspirin-treated patients experienced a greater frequency of withdrawal from the study because of adverse experiences (34 percent versus 13 percent), a greater incidence of having at least one treatment-related adverse experience (73 percent versus 52 percent), a greater percentage of patients with at least one moderate or severe treatment-related adverse experience (47 percent versus 22 percent), and a greater percentage of patients with treatment-related adverse experiences affecting the gastrointestinal system (43 percent versus 32 percent) or the inner ear (32 percent versus 10 percent). The results of this study demonstrated that nabumetone, 1,000 mg at bedtime, is as efficacious as aspirin, 900 mg four times daily, produces fewer adverse effects, and is indicated in the treatment of osteoarthritis.

See Fries JF, Ramey DR, Singh G, Morfeld D, Bloch DA, Raynauld JP, "A reevaluation of aspirin therapy in rheumatoid arthritis", Arch Intern Med. 1993 Nov 8;153(21):2465-2471.

The abstract of the preceding reference (Fries et al.) is as follows:

"Aspirin therapy has been largely superseded by prescription nonsteroidal anti-inflammatory drug (NSAID) therapy in rheumatoid arthritis, in part because of premarketing studies suggesting lesser toxic effects for NSAIDs than for aspirin. This study evaluates these toxic effects in a postmarketing population of patients with rheumatoid arthritis. METHODS: We studied 1521 consecutive courses of aspirin and 4860 courses of NSAIDs in patients with rheumatoid arthritis from eight Arthritis, Rheumatism, and Aging Medical Information System Post-marketing Surveillance Centers. Toxicity index scores were generated from symptoms, laboratory abnormalities, and hospitalizations, weighted for variable severity and severity of side effect. RESULTS: The toxicity index was only 1.37 (SE = 0.10) for aspirin and 1.87 to 2.90 for selected nonsalicylate NSAIDs. These differences were consistent across centers and remained after statistical adjustment for differing patient characteristics. There was a different toxicity with different aspirin preparations, with a score for plain aspirin of 1.36 (SE = 0.23), for buffered aspirin of 1.10 (0.20), and for enteric-coated aspirin preparations of 0.92 (0.14). Most important, there were strong dose effects, with a score of 0.73 (0.09) for 651 to 2600 mg daily, 1.08 (0.17) for 2601 to 3900 mg, and 1.91 (0.38) for more than 3900 mg. The average aspirin dose taken was only 2665 mg/d, approximately eight "tablets," compared with 3600 to 4800 mg/d used in the 16 pivotal premarketing studies reviewed. Average NSAID doses were, on the other hand, lower in premarketing trials (eg, naproxen 500 mg/d vs 773 mg/d in the Arthritis, Rheumatism, and Aging Medical System clinical practices). CONCLUSIONS: Aspirin therapy, in doses commonly employed in practice, has an excellent safety profile in rheumatoid arthritis, and it is the least costly NSAID. The safety advantage is explained primarily by a dose effect and secondarily by possible differences between formulations. Newer management strategies for rheumatoid arthritis emphasize NSAID use as symptomatic therapy and use of disease-modifying anti-rheumatic drug therapy for anti-inflammatory objectives.

Thus, the original recommendation for "anti-inflammatory" doses of aspirin now is less easily justified. Aspirin therapy merits reconsideration as adjunctive therapy for the management of rheumatoid arthritis."

See Edwards, W., "Etodolac, aspirin, and placebo in patients with rheumatoid arthritis: a 12-week study", Clin Ther. 1983;5(5):495-503. The abstract of the preceding reference (Edwards) is as follows:

"Etodolac, aspirin, and placebo were evaluated for efficacy and safety in 18 patients with adult-onset, active rheumatoid arthritis. This was a 12-week, double-blind, parallel-group study divided into drug titration and maintenance periods and preceded by a washout period of up to two weeks. The mean daily maintenance doses of etodolac and aspirin were 394 mg and 4,414 mg, respectively. Etodolac was significantly (P less than or equal to 0.05) more effective than placebo in five of ten clinical variables of efficacy: number of painful joints, number of swollen joints, pain intensity, erythrocyte sedimentation rate, and patients' overall assessments. Aspirin was significantly more effective than placebo in only two assessments: number of painful joints and pain intensity. One patient on etodolac, two patients on aspirin, and four patients on placebo had to be withdrawn from the trial because of insufficient therapeutic response. One patient in the placebo group was withdrawn from the study because of a pruritic rash. Mild to moderate gastrointestinal complaints occurred in all three treatment groups: in three patients taking etodolac, three taking aspirin, and two taking placebo."

See Kolarz G., "Double-blind, cross-over, international multicentre investigation of two doses of indoprofen compared with ASA and placebo in rheumatoid arthritis", Eur J Rheumatol Inflamm., 1981;4(1):53-59. The abstract of the preceding reference (Kolarz) is as follows:

"Indoprofen 600 mg or 1000 mg/day, ASA 3600 mg/day and placebo were administered in randomized sequences according to a multiple 4 x 4 latin square design, balancing the treatments, periods and residual effects. Each treatment lasted 7 days. A total of 98 patients suffering from classical or definite rheumatoid arthritis completed the study. Analysis of the effectiveness indicates that both doses of indoprofen and ASA are significantly more active than placebo; indoprofen 1000 mg/day was the treatment preferred in most of the cases. Both doses of indoprofen were better tolerated than ASA."

In summary, the preceding evidence demonstrates that aspirin doses of 394 mg to 6,000 mg are therapeutically effective in the treatment of inflammatory disorder. The Examiner has not provided any credible scientific evidence that low dose aspirin in doses of 30-75 mg is therapeutically effective in the treatment of inflammatory disorder.

A second reason why claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro is that Hedden in view of Langhoff and Shapiro does not teach or suggest the feature: "an antioxidant selected from the group consisting of a flavanoid, a flavonoid, an isoflavone, and combinations thereof".

The Examiner argues: "Shapiro (US 6444221) teaches the use of flavonoids, flavanoids and isoflavones (i.e., daidzin, genistein, quercetin, silymarin, etc...) as antioxidants having functional equivalent property for the treatment of inflammatory disease conditions (column 9, line 52 thru column 19, line 32; column 20, line 47 thru column 21, line 8)."

In response, Applicants contend that Shapiro teaches that the disclosed flavonoids, flavanoids and isoflavones as antioxidants are useful in treating of inflammatory disease only in

combination with carbonyl trapping agents. See Shapiro, col, 10, lines 43-51. See also, Shapiro, col, 10, lines 59-67 ("In another preferred embodiment, use of a primary agent in combination with a clinically effective anti-oxidant and lipid peroxidation inhibitor co-agent may be of particular benefit in preventing or ameliorating forms of chronic inflammation by incorporating two pharmacological strategies, the sequestering of cytotoxic aldehydes and ketones generated at sites of chronic inflammation and the sequestering of activated oxygen chemical species generated earlier in the non-enzymatic inflammatory cascade.").

In Shapiro's composition, the carbonyl trapping agent is the primary ingredient and the antioxidant in one of several alternative secondary ingredients. Shapiro does not teach that the antioxidant by itself is therapeutically effective in treating inflammatory disease.

Therefore, Applicants respectfully contend that Shapiro does not teach that the disclosed flavonoids, flavanoids and isoflavones as antioxidants are useful in treating of inflammatory disease in combination with low dose aspirin and COX2 inhibitor, since aspirin and COX2 inhibitor are not carbonyl trapping agents. Accordingly, it would not be obvious to add the disclosed flavonoids, flavanoids and isoflavones as antioxidants to Lai's composition of aspirin and COX2 inhibitor for the purpose of treating of inflammatory disease.

Based on the preceding arguments, Applicants respectfully maintain that claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro, and that claims 10 and 18 are in condition for allowance. Since claims 11-13 and 24 depend from claim 10, Applicants contend that claims 11-13 and 24 are likewise in condition for allowance. Since claims 19-21 and 23 depend from claim 18, Applicants contend that claims 19-21 and 23 are likewise in condition for allowance.

The Examiner rejected claims 15 and 22 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221), and further in view of Burch *et al.* (US 6,552,031) and Drug Facts and Comparison (1995 Edition, pp. 1248) and Hendeler (US 6,541,613B2).

Since claims 15 and 22 respectively depend from claims 10 and 18, which Applicants have argued *supra* to not be unpatentable over Hedden in view of Langhoff and Shapiro under 35 U.S.C. §103(a), Applicants maintain that claims 15 and 22 are likewise not unpatentable over Hedden in view of Langhoff and Shapiro Jones in view of Smith and further in view of Burch, Drug Facts and Comparison, and Hendeler under 35 U.S.C. §103(a).

**CONCLUSION**

Based on the preceding arguments, Applicants respectfully believe that all pending claims and the entire application meet the acceptance criteria for allowance and therefore request favorable action. If the Examiner believes that anything further would be helpful to place the application in better condition for allowance, Applicants invites the Examiner to contact Applicants' representative at the telephone number listed below. The Director is hereby authorized to charge and/or credit Deposit Account No. 19-0513.

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